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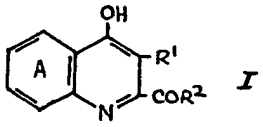
(54) PHARMACEUTICAL COMPOSITIONS CONTAINING KYNURENIC ACID DERIVATIVES

(71) We, IMPERIAL CHEMICAL INDUSTRIES LIMITED, of Imperial Chemical House, Millbank, London, S.W.1., a British Company, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to new pharmaceutical compositions and to new compounds, and more particularly it relates to pharmaceutical compositions containing kynurenic acid derivatives which are active as inhibitors of the effects following the combination of reagin-like antibodies and their antigens, and it also relates to new kynurenic acid derivatives and the manufacture thereof. The said compositions and compounds are useful in the treatment of allergic asthma in man. Also, they are useful in the treatment of other syndromes initiated by an antigen-antibody reaction, for example hay fever, urticaria and auto-immune diseases.

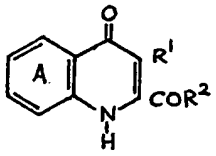
According to the invention there are provided pharmaceutical compositions comprising a compound of the formula:—



I

wherein R^1 stands for hydrogen, a methyl or ethyl radical or a halogen atom, R^2 stands for a hydroxy or C_{1-6} alkoxy radical, and the benzene ring A may optionally bear not more than two substituents selected from C_{1-5} alkyl, C_{1-5} alkoxy, benzyl, phenyl, benzyloxy, acetyl, halogen, trifluoromethyl, nitro and amino (—NH_2) radicals, or wherein the said benzene ring A may optionally be fused with an unsubstituted benzene ring, a methoxy-substituted-benzene ring or a tetramethylene radical, or a non-toxic pharmaceutically-acceptable salt thereof, and an inert non-toxic pharmaceutically-acceptable diluent or carrier.

It is to be understood that the said compounds of formula I can exist in the tautomeric form having the general formula:—



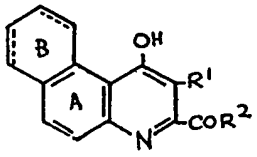
II

wherein R^1, R^2 and A have the meanings stated above, but for convenience in this specification they will all be referred to as 4-hydroxyquinoline derivatives.

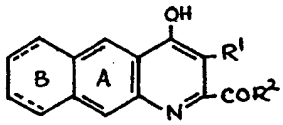
As a suitable value for R^1 there may be mentioned hydrogen or a methyl or ethyl radical or a fluorine, chlorine, bromine or iodine atom. As a suitable value for R^2 when it stands for a C_{1-6} alkoxy radical there may be mentioned, for example, a methoxy or ethoxy radical.

The benzene ring A may optionally bear one or two substituents selected from, for example, methyl, ethyl, propyl, butyl, methoxy, ethoxy, propoxy, butoxy, benzyl, phenyl, benzyloxy, acetyl, fluorine, chlorine, bromine, iodine, trifluoromethyl, nitro and amino radicals, or it may optionally be fused with an unsubstituted benzene ring, a methoxy-substituted-benzene ring or a tetramethylene radical.

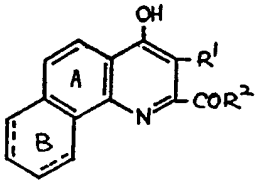
It is to be understood that the said compounds of formula I in which the benzene ring A is fused with an unsubstituted benzene ring, a methoxy-substituted-benzene ring, or a tetramethylene radical, fall into three general classes, having the following formulae:—



III

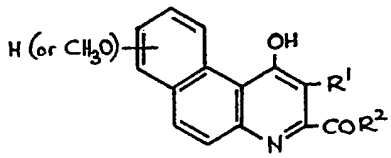


IV



V

wherein ring B signifies one of the abovementioned fused substituents. In particular there may be mentioned compounds of the formula:—



VI

wherein R^1 and R^2 have the meanings stated above, and non-toxic pharmaceutically-acceptable salts thereof, for example 1-hydroxy-8-methoxybenzo(f)quinol-3-yl carboxylic acid.

Suitable salts of the invention in the case where the said compounds of formula I are sufficiently basic are non-toxic pharmaceutically-acceptable acid-addition salts derived from inorganic or organic acids; examples are hydrochlorides, hydrobromides, tartrates or citrates. Suitable salts of the invention in the case where R^2 stands for a hydroxy radical are salts in which the cationic moiety is non-toxic and pharmaceutically-acceptable, for example ammonium salts, alkali metal salts, alkaline earth metal salts, aluminium salts or salts with pharmaceutically-acceptable organic bases, for example piperidine, triethanolamine or ethylenediamine.

Specific known compounds which are preferred compounds for use as active ingredients in the pharmaceutical compositions of the invention are 4-hydroxy-8-nitroquinol-2-yl carboxylic acid, and 1-hydroxybenzo(f)quinol-3-yl carboxylic acid.

Specific new compounds which are preferred compounds for use as active ingredients in the pharmaceutical compositions of the invention are 4-hydroxy-7,8-dimethylquinol-2-yl carboxylic acid and 4-hydroxy-7-methylquinol-2-yl carboxylic acid.

The pharmaceutical compositions of the invention comprise conventional diluents or carriers and they can be obtained by well known methods.

The compounds of formula I are particularly useful for the treatment of allergic asthma, and for this purpose the said compositions are preferably in a form suitable for administration by inhalation. Suitable compositions comprise a mixture of the active ingredient with a solid diluent or carrier, for example lactose, the said mixture being in fine particulate form suitable for administration from a powder inhalation device. Alternatively, the compositions may be administered in the form of a suspension or solution in a suitable liquid, for example water or an aqueous or non-aqueous medium, for administration using a conventional nebulizer or a pressurised container.

The pharmaceutical compositions of the invention may also contain, in addition to a compound of formula I, one or more other active ingredients selected from a β-adrenergic stimulant, for example isoprenaline, adrenaline, orciprenaline, isoethacine, or a pharmaceutically-acceptable acid-addition salt thereof, for example a sulphate, or a known prostaglandin having bronchodilatory activity, for example prostaglandin E_1 or E_2, and/or a phosphodiesterase inhibitor selected from the following compounds:—

(a) 3-acetamido-6-methyl-8-n-propyl-s-triazolo[4,3-a]pyrazine;
(b) 2-amino-4,6-di-C_{1-4}-alkyl-5-oxo-4,5-dihydro-s-triazolo-[1,5-a]pyrimidine derivatives, for example 2-amino-6-methyl-5-oxo-4-n-propyl-4,5-dihydro-s-triazolo [1,5-a]pyrimidine;
(c) theophylline or a related 3,5-di-C_{1-4}-alkylxanthine derivative; and
(d) 6,8-di-C_{1-4}-alkyl-5,6-dihydro-5-oxo-s-triazolo[4,3-c]pyrimidine derivatives, for example 5,6-dihydro-5-oxo-6,8-di-n-propyl-s-triazolo[4,3-c]pyrimidine.

The pharmaceutical compositions of this invention may contain from 1% to 50% by weight of a compound of formula I. In use in man, for example for the treatment of asthma, the dose of a compound of formula I will be from 0.01 to 1mg./kg., at suitable intervals when relief or prevention of allergic airway obstruction is required.

As stated above, the compounds of formula I, wherein A, R^1 and R^2 have the meanings stated above, and the non-toxic pharmaceutically-acceptable salts thereof, have useful biological properties. Furthermore, as indicated below, the compounds of formula I wherein R^2 stands for a C_{1-6} alkoxy radical are also useful as intermediates for the manufacture, by hydrolysis, of the corresponding acids. The majority of the compounds of formula I are new compounds, and these new compounds constitute a further feature of this invention.

According to a further feature of the invention, therefore, there are provided compounds of the formula I wherein R^1 stands for hydrogen or a methyl or ethyl radical, R^2 stands for a hydroxy or C_{1-6} alkoxy radical, and the benzene ring A is optionally substituted with not more than two substituents selected from C_{1-5} alkyl, C_{1-5} alkoxy, benzyl, benzyloxy, acetyl, halogen, trifluoromethyl, nitro or amino ($-NH_2$) radicals, or wherein the benzene ring A is optionally fused in the 5,6- or 7,8-position with an unsubstituted benzene ring, a methoxy-substituted-benzene ring, or a tetramethylene radical, and non-toxic pharmaceutically-acceptable salts thereof; but excluding the following known compounds:—

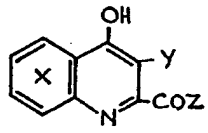
4-hydroxyquinol-2-yl carboxylic acid and its methyl ester, 4-hydroxy-8-methylquinol-2-yl carboxylic acid, 4-hydroxy-6-methylquinol-2-yl carboxylic acid and its ethyl ester, methyl 4-hydroxy-6,8-dimethylquinol-2-yl carboxylate, 4-hydroxy-7-methoxyquinol-2-yl carboxylic acid, 4-hydroxy-6-methoxyquinol-2-yl carboxylic acid and its ethyl ester,

4-hydroxy-8-methoxyquinol-2-yl carboxylic acid and its methyl and ethyl esters, 4-hydroxy-5,6-dimethoxyquinol-2-yl carboxylic acid and its ethyl ester, 4-hydroxy-5,8-dimethoxyquinol-2-yl carboxylic acid and its ethyl ester, 4-hydroxy-6,7-dimethoxyquinol-2-yl carboxylic acid and its methyl and ethyl esters, ethyl 4-hydroxy-7,8-dimethoxyquinol-2-yl carboxylate, 6-bromo-4-hydroxyquinol-2-yl carboxylic acid, 7-bromo-4-hydroxyquinol-2-yl carboxylic acid and its ethyl ester, 8-bromo-4-hydroxyquinol-2-yl carboxylic acid, 5-chloro-4-hydroxyquinol-2-yl carboxylic acid and its methyl and ethyl esters, 6-chloro-4-hydroxyquinol-2-yl carboxylic acid and its methyl ester, 7-chloro-4-hydroxyquinol-2-yl carboxylic acid and its methyl and ethyl esters, methyl 8-chloro-4-hydroxyquinol-2-yl carboxylate, 4-hydroxy-7-iodoquinol-2-yl carboxylic acid and its ethyl ester, methyl and ethyl 6-fluoro-4-hydroxyquinol-2-yl carboxylate, 5,7-dibromo-4-hydroxyquinol-2-yl carboxylic acid and its ethyl ester, 5,6-dichloro-4-hydroxyquinol-2-yl carboxylic acid and its ethyl ester, 5,7-dichloro-4-hydroxyquinol-2-yl carboxylic acid and its methyl and ethyl esters, 5,8-dichloro-4-hydroxyquinol-2-yl carboxylic acid and its ethyl ester, 6,7-dichloro-4-hydroxyquinol-2-yl carboxylic acid and its ethyl ester, 6,8-dichloro-4-hydroxyquinol-2-yl carboxylic acid and its ethyl ester, 4-hydroxy-3-methylquinol-2-yl carboxylic acid, 1-hydroxybenzo(f)quinol-3-yl carboxylic acid and its ethyl ester, 1-hydroxy-7-methoxybenzo(f)quinol-3-yl carboxylic acid and its ethyl ester, 1-hydroxy-10-methoxybenzo(f)quinol-3-yl carboxylic acid and its ethyl ester, ethyl 1-hydroxy-8-methoxybenzo(f)quinol-3-yl carboxylate, 4-hydroxybenzo(h)quinol-2-yl carboxylic acid and its ethyl ester, 4-hydroxy-6-methoxybenzo(h)quinol-2-yl carboxylic acid and its ethyl ester, 7,8,9,10-tetrahydro-4-hydroxy-6-methoxybenzo(h)quinol-2-yl carboxylic acid and its ethyl ester, 4-hydroxy-7-methoxy-8-nitroquinol-2-yl carboxylic acid, 5-amino-4-hydroxyquinol-2-yl carboxylic acid, 6-amino-4-hydroxyquinol-2-yl carboxylic acid, 7-chloro-4-hydroxy-6-methoxyquinol-2-yl carboxylic acid and its methyl and ethyl esters, methyl 8-acetyl-4-hydroxyquinol-2-yl carboxylate, 6-acetyl-4-hydroxyquinol-2-yl carboxylic acid and its ethyl ester, methyl 6-chloro-4-hydroxy-8-nitroquinol-2-yl carboxylate, 4-hydroxy-6-methoxy-8-nitroquinol-2-yl carboxylic acid and its methyl ester, methyl 4-hydroxy-6-methyl-8-nitroquinol-2-yl carboxylate, methyl and ethyl 4-hydroxy-6-nitroquinol-2-yl carboxylate, methyl 4-hydroxy-7-nitroquinol-2-yl carboxylate, 4-hydroxy-8-nitroquinol-2-yl carboxylic acid and its methyl ester, 6-benzyl-4-hydroxyquinol-2-yl carboxylic acid and its ethyl ester, 7-chloro-4-hydroxy-8-methylquinol-2-yl carboxylic acid and its ethyl ester, 5-bromo-4-hydroxy-6-methoxyquinol-2-yl carboxylic acid and its ethyl ester, 7-bromo-4-hydroxy-6-methoxyquinol-2-yl carboxylic acid and its ethyl ester, 4-hydroxy-5-iodo-8-methoxyquinol-2-yl carboxylic acid, methyl 4-hydroxy-6-methoxy-7-trifluoromethylquinol-2-yl carboxylate, methyl 8-chloro-4-hydroxy-5-trifluoromethylquinol-2-yl carboxylate, methyl 5-chloro-4-hydroxy-6-methoxyquinol-2-yl carboxylate, methyl 7-fluoro-4-hydroxy-6-methoxyquinol-2-yl carboxylate, 4-hydroxy-3,5-dimethylquinol-2-yl carboxylic acid and its ethyl ester, 4-hydroxy-3,6-dimethylquinol-2-yl carboxylic acid and its ethyl ester, 4-hydroxy-3,7-dimethylquinol-2-yl carboxylic acid and its ethyl ester, 4-hydroxy-3,8-dimethylquinol-2-yl carboxylic acid and its ethyl ester, 4-hydroxy-3,5,6-trimethylquinol-2-yl carboxylic acid and its ethyl ester, 4-hydroxy-3,6,7-trimethylquinol-2-yl carboxylic acid, ethyl 4-hydroxy-3,6,8-trimethylquinol-2-yl carboxylate, 6-ethoxy-4-hydroxy-3-methylquinol-2-yl carboxylic acid and its ethyl ester, 8-ethoxy-4-hydroxy-3-methylquinol-2-yl carboxylic acid and its ethyl ester, 7-ethoxy-4-hydroxy-3-methylquinol-2-yl carboxylic acid and its ethyl ester, 4-hydroxy-7-methoxy-3-methylquinol-2-yl carboxylic acid and its ethyl ester, 4-hydroxy-8-methoxy-3-methylquinol-2-yl carboxylic acid and its ethyl ester, ethyl 4-hydroxy-6,8-dimethoxy-3-methylquinol-2-yl carboxylate, 5-bromo-4-hydroxy-3-methylquinol-2-yl carboxylic acid and its ethyl ester, 5-chloro-4-hydroxy-3-methylquinol-2-yl carboxylic acid and its ethyl ester, 7-bromo-4-hydroxy-3-methylquinol-2-yl carboxylic acid and its ethyl ester, 7-chloro-4-hydroxy-3-methylquinol-2-yl carboxylic acid and its ethyl ester, 6-chloro-4-hydroxy-3-methylquinol-2-yl carboxylic acid, 6-bromo-4-hydroxy-3-methylquinol-2-yl carboxylic acid and its ethyl ester, 8-chloro-4-hydroxy-3-methylquinol-2-yl carboxylic acid and its ethyl ester, 8-bromo-4-hydroxy-3-methylquinol-2-yl carboxylic acid and its ethyl ester, ethyl 4-hydroxy-5-iodo-3-methylquinol-2-yl carboxylate, 4-hydroxy-6-iodo-3-methylquinol-2-yl carboxylic acid and its ethyl ester, 4-hydroxy-7-iodo-3-methylquinol-2-yl carboxylic acid and its ethyl ester, 4-hydroxy-8-iodo-3-methylquinol-2-yl carboxylic acid and its ethyl ester, 5-fluoro-4-hydroxy-3-methylquinol-2-yl carboxylic acid and its ethyl ester, 6-fluoro-4-hydroxy-3-methylquinol-2-yl carboxylic acid and its ethyl ester, 7-fluoro-4-hydroxy-3-methylquinol-2-yl carboxylic acid and its ethyl ester, 8-fluoro-4-hydroxy-3-methylquinol-2-yl carboxylic acid and its ethyl ester, 8-chloro-4-hydroxy-3,5-dimethylquinol-2-yl carboxylic acid and its ethyl ester, 4-hydroxy-3-methyl-5-trifluoromethylquinol-2-yl carboxylic acid

and its ethyl ester, 4-hydroxy-3-methyl-7-trifluoromethylquinol-2-yl carboxylic acid and its ethyl ester, ethyl 4-hydroxy-3-methyl-5-nitroquinol-2-yl carboxylate, 4-hydroxy-3-methyl-6-nitroquinol-2-yl carboxylic acid and its ethyl ester, and ethyl 4-hydroxy-3-methyl-7-nitroquinol-2-yl carboxylate.

Particularly preferred new compounds are the two specific new compounds which are mentioned above, and non-toxic pharmaceutically-acceptable salts thereof.

It is to be understood that for convenience the abovementioned new compounds of the invention will be referred to collectively hereinafter by the following formula:—

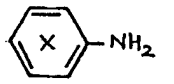


VII

wherein X, Y and Z correspond to A, R^1 and R^2 respectively.

The new C_{1-6} alkyl esters of the invention may be obtained by means of the Conrad-Limpach reaction or, in the case of some of said esters, by the related process described below which involves an ester of acetylene dicarboxylic acid.

According to a further feature of the invention therefore there is provided a process for the manufacture of compounds of formula VII wherein Z stands for a C_{1-6} alkoxy radical, which comprises reacting an arylamine of the formula:—



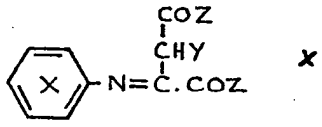
VIII

with a compound of the formula:—

Z.CO.CHY.CO.COZ IX

wherein X and Y have the meanings stated above and Z has the meaning stated immediately above (the Conrad-Limpach reaction).

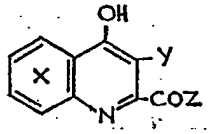
This process involves two stages. In the first stage there is formed a compound which in one of its tautomeric forms has the formula:—



X

This stage may, for example, be carried out at an elevated temperature, for example a temperature of 80—100°C., in an aromatic hydrocarbon solvent, for example benzene, under reaction conditions which facilitate the removal of water from the reaction mixture, for example in a Dean and Stark apparatus.

The second stage of the Conrad-Limpach reaction involves ring-closing the compound of formula X so as to obtain a compound of the formula:—



VII

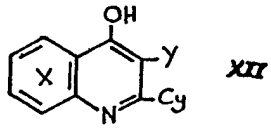
wherein X, Y and Z have the meanings stated immediately above. The said second stage may, for example, be carried out either by heating the compound of formula X at 230—250°C., for example in diphenyl ether or α-chloronaphthalene, or by reacting the compound of formula X with polyphosphoric acid at 130—180°C., for example about 150°C.

According to a further feature of the invention there is provided a process for the manufacture of compounds of the formula VII wherein Y stands for hydrogen and Z stands for a C_{1-6} alkoxy radical, which comprises reacting an arylamine of the formula VIII with an acetylene derivative of the formula:—

$$ZOC.C{\equiv}C.COZ \qquad XI$$

wherein Z has the meaning stated immediately above, in the presence of an alkanol of the formula ZOH, for example methanol, and, following an optional initial stage during which the temperature of the reaction mixture is not allowed to exceed 30°C., under the influence of heat, for example under reflux, so as to give a compound which in one of its tautomeric forms has the formula X wherein Y stands for hydrogen, and then ring-closing this compound, for example by either of the methods described above, to give the desired product of formula VII.

According to a further feature of the invention there is provided a process for the manufacture of compounds of the formula VII wherein Z stands for a hydroxy radical, which comprises hydrolysing a compound of the formula:—



XII

wherein X and Y have the meanings stated above, and Cy stands for a C_{2-7} alkoxycarbonyl, C_{8-11} phenylalkoxycarbonyl, phenoxycarbonyl, cyano, carbamoyl ($—CONH_2$) or thiocarbamoyl ($—CSNH_2$) radical.

As a suitable hydrolytic agent there may be mentioned, for example, an alkali metal hydroxide, for example sodium hydroxide, or an inorganic acid, for example sulphuric acid.

According to a further feature of the invention there is provided a process for the manufacture of those of the new compounds of formula VII wherein Z stands for a C_{1-6} alkoxy radical and the benzene ring X bears one or two amino radicals, which comprises catalytically reducing the nitro group(s) in the corresponding nitro derivative.

It is to be understood that the starting materials used in the processes of this invention are obtainable by means of general reactions which are known to those skilled in the art.

The invention is illustrated by the following Examples:—

Example 1.

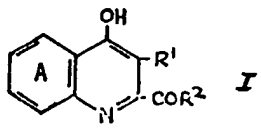
An aerosol formulation was prepared consisting of finely divided 4-hydroxy-8-methylquinol-2-yl carboxylic acid 2% w/w (screened through mesh size 90; British Standard 410: 1962), isoprenaline sulphate 0.1% w/w (screened through mesh size 90), and propellant to 100% w/w (the propellant was a 60:40 v/v mixture of dichloro-difluoromethane and 1,2-dichloro-1,1,2,2-tetrafluoroethane).

Example 2.

4-Hydroxy-8-methylquinol-2-yl carboxylic acid (20g.; screened through mesh size 90), isoprenaline sulphate (0.1g.; screened through mesh size 90) and lactose (15g.; screened through mesh size 90) were thoroughly mixed. There was thus obtained a powder formulation suitable for inhalation for medicinal purposes.

Example 3.

The method described in Example 2 was repeated except that the 4-hydroxy-8-methylquinol-2-yl carboxylic acid was replaced by the same amount of either 1-hydroxy-8-methoxybenzo(f)quinol-3-yl carboxylic acid or one of the following compounds:—



I

A	R¹	R²	A	R¹	R²
6-Br	H	OH	7,8-$(CH_2)_4$	H	OH
5,8-Cl_2	H	OH	5-Me	H	OH
6,8-Cl_2	H	OH	7-Me	H	OH
6-MeO	H	OH	8-NO_2	H	OH
8-Ph	H	OH	6-Me	H	OH
5,8-Me_2	H	OH	7-NO_2	H	OH
6,7-Me_2	H	OH	8-Et	H	OH
6-$PhCH_2O$	H	OH	6-Et	H	OH
7-MeO	H	OH	8-Cl	H	OH
8-MeO	H	OH	6,8-Br_2	H	OH
6-F	H	OH	8-CF_3	H	OH
5-Cl-8-Me	H	OH	8-Br	H	OH
7,8-benz	H	OH	5,8-Br_2	H	OH
			8-F	H	OH
7,8-Me_2	H	OH	5,7-Cl_2	H	OH
7,8-Me_2	H	OEt	6-Cl-8-Me	H	OH
8-n-BuO	H	OH	5-NO_2-8-EtO	H	OH
8-n-BuO	H	OEt	5-NO_2-8-EtO	H	OMe
6-n-Bu	H	OH	5-NH_2-8-EtO	H	OH
6-n-Bu	H	OEt	5-NH_2-8-EtO	H	OMe
6-Me-8-Br	H	OH	6-I	H	OH
H	H	OH	H	3-Br	OH
			6-CH_3CO—	H	OH
7-Cl	H	OH	5-Cl	3-Me	OH
6-Cl	H	OH	6,7-$(Pr^iO)_2$	H	OH
5-Cl	H	OH	6-CH_3CO	3-Et	OH
7-Cl	3-I	OH	6-$PhCH_2$	H	OH
8-I	H	OH			

There were thus obtained powder formulations suitable for inhalation for medicinal purposes.

Example 4.

Ethyl 4-hydroxy-7,8-dimethylquinol-2-yl carboxylate (1g.; see Example 9) was boiled with 10% (w/v) aqueous sodium hydroxide (10ml.) for 15 minutes. After cooling, the solution was acidified with dilute aqueous hydrochloric acid to pH 2 and the resultant precipitate was collected by filtration, washed with water, dried at 100°C. and successively crystallised from methanol and dimethylformamide. There was thus obtained 4-hydroxy-7,8-dimethylquinol-2-yl carboxylic acid, m.p. 275—276°C. (decomposition).

Example 5.

The method described in Example 4 was repeated using the appropriate starting materials, and the following compounds were obtained: —
6-acetyl-3-ethyl-4-hydroxyquinol-2-yl carboxylic acid, m.p. 260°C. (decomposition);
6-acetyl-4-hydroxy-3-methylquinol-2-yl carboxylic acid, m.p. 268—269°C. (decomposition);
6-benzyloxy-4-hydroxyquinol-2-yl carboxylic acid, m.p. 287°C. (decomposition);
8-n-butoxy-4-hydroxyquinol-2-yl carboxylic acid, m.p. 257°C. (decomposition);
5-chloro-4-hydroxy-8-methylquinol-2-yl carboxylic acid, m.p. 269°C. (decomposition);
4-hydroxy-6-iodoquinol-2-yl carboxylic acid, m.p. 308°C. (decomposition);
4-hydroxy-8-iodoquinol-2-yl carboxylic acid, m.p. 260°C. (decomposition);
4-hydroxy-8-methoxy-5-methylquinol-2-yl carboxylic acid, m.p. 273°C. (decomposition);
4-hydroxy-6,8-dimethylquinol-2-yl carboxylic acid, m.p. 260—260.5°C. (decomposition);
4-hydroxy-6,7-dimethylquinol-2-yl carboxylic acid, m.p. 262°C. (decomposition);
4-hydroxy-7-trifluoromethylquinol-2-yl carboxylic acid, m.p. 277°C. (decomposition);
4-hydroxy-5-methylquinol-2-yl carboxylic acid, m.p. 297°C. (decomposition);
4-hydroxy-7-methylquinol-2-yl carboxylic acid, m.p. 293°C. (decomposition); and
4-hydroxy-5,8-dimethylquinol-2-yl carboxylic acid, m.p. 278°C. (decomposition).

Example 6.

The method described in Example 4 was repeated using the appropriate starting materials, and the following compounds were obtained: —
6-n-butyl-4-hydroxyquinol-2-yl carboxylic acid, m.p. 271°C. (decomposition);
6-chloro-4-hydroxy-8-methylquinol-2-yl carboxylic acid, m.p. 276°C. (decomposition);
7,8,9,10-tetrahydro-4-hydroxybenzo(h)quinol-2-yl carboxylic acid, m.p. 279°C. (decomposition);
6-fluoro-4-hydroxyquinol-2-yl carboxylic acid, m.p. 304°C. (decomposition); and
8-bromo-4-hydroxy-6-methylquinol-3-yl carboxylic acid, m.p. 269°C. (decomposition).

Example 7.

A solution comprising methyl 8-methyl-4-hydroxyquinol-2-yl carboxylate (obtained as described in Example 11) was basified to pH 12 with 4N sodium hydroxide. The mixture was heated on a steam bath for 1½ hours. The solution was filtered through kieselguhr, and the clear filtrate was acidified to pH 1 with concentrated hydrochloric acid. The resulting precipitate was filtered off, washed with water, and crystallised from 50% v/v aqueous dimethylformamide to give 8-ethyl-4-hydroxyquinol-2-yl carboxylic acid, m.p. 242°C. (decomposition).

In a similar manner, using the appropriate starting materials, the following compounds were obtained: —
6-ethyl-4-hydroxyquinol-2-yl carboxylic acid, m.p. 262°C. (decomposition);
8-chloro-4-hydroxyquinol-2-yl carboxylic acid, m.p. 260°C. (decomposition);
6,8-dibromo-4-hydroxyquinol-2-yl carboxylic acid, m.p. 284°C. (decomposition);
4-hydroxy-8-trifluoromethylquinol-2-yl carboxylic acid, m.p. 231°C. (decomposition);
5,8-dibromo-4-hydroxyquinol-2-yl carboxylic acid, m.p. 269°C. (decomposition);
8-fluoro-4-hydroxyquinol-2-yl carboxylic acid, m.p. 261°C. (decomposition); and
4-hydroxy-7-nitroquinol-2-yl carboxylic acid, containing one mole of dimethylformamide of crystallisation, m.p. 294°C. (decomposition).

Example 8.

Ethyl 4-hydroxy-5-methylquinol-2-yl carboxylate (1.0g.) was hydrolysed by heating at 100°C. for 5 minutes together with 2N sodium hydroxide solution (20 ml.). The mixture was then acidified to pH 1 with 4N hydrochloric acid, and the resulting

precipitate filtered off. There was thus obtained 4-hydroxy-5-methylquinol-2-yl carboxylic acid, m.p. 297°C. (decomposition).

In the same way, but using the corresponding 7-methyl compound as the starting material, there was obtained 4-hydroxy-7-methylquinol-2-yl carboxylic acid, m.p. 293°C. (decomposition).

Example 9.

Sodio diethyloxaloacetate (15.8g.) was added in portions of *ca* 2g. to a stirred mixture of 10N hydrochloric acid (10 ml.), water (100 ml.) and benzene (50 ml.) at a temperature not exceeding 20°C. The mixture was stirred for 1 hour, and the benzene layer was separated and washed with water (50ml.). The aqueous washings were back-extracted with benzene (50ml.) and the combined benzene solutions were dried over anhydrous magnesium sulphate and filtered. 2,3-Dimethylaniline (6g.) was added and the mixture boiled in an apparatus for continuously removing water from the reaction mixture (a Dean and Stark apparatus) until no more water was collected. The benzene was removed *in vacuo* and the residue (a crude crotonate) was added dropwise over 5 minutes to boiling α-chloronaphthalene (250 ml.). The mixture was heated at 250—260°C. until no more ethanol was liberated (about 5 minutes). The solution was cooled to room temperature and diluted by the addition of petroleum ether (b.p. 100—120°C.; 750ml.). After standing for 30 minutes, the suspension was filtered and the solid residue washed with 6 portions of petroleum ether (b.p. 40—60°C.; each portion 50ml.). There was thus obtained, as solid residue, ethyl 4-hydroxy-7,8-dimethylquinol-2-yl carboxylate, m.p. 136—142°C.

Example 10.

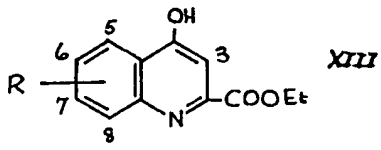
Dimethyl acetylene dicarboxylate (5.9g.) was added dropwise to a stirred solution of 2-ethylaniline (5.0g.) in methanol (50ml.) at a rate such that the temperature did not exceed 30°C. When the addition was complete the solution was heated under reflux for 3 hours, and then cooled and the methanol evaporated off under reduced pressure, leaving a red oil. This was added to polyphosphoric acid (100 ml.) and the mixture was stirred and heated in an oil bath at 180°C. for 30 minutes. The mixture was cooled and poured into water (500ml.). There was thus obtained a solution comprising methyl 8-ethyl-4-hydroxyquinol-2-yl carboxylate.

In a similar manner, using the appropriate starting materials, there were obtained solutions comprising the following compounds:—
methyl 6-ethyl-4-hydroxyquinol-2-yl carboxylate;
methyl 8-chloro-4-hydroxyquinol-2- carboxylate;
methyl 6,8-dibromo-4-hydroxyquinol-2-yl carboxylate;
methyl 4-hydroxy-8-trifluoromethylquinol-2-yl carboxylate;
methyl 5,8-dibromo-4-hydroxyquinol-2-yl carboxylate;
methyl 8-fluoro-4-hydroxyquinol-2-yl carboxylate; and
methyl 4-hydroxy-7-nitroquinol-2-yl carboxylate.

Example 11.

Sodium diethyl oxaloacetate (26.0g.) was added in portions of *ca* 2g. to 10N hydrochloric acid (10.9ml.) in water 200ml.). Benzene (200 ml.) was added, the mixture was shaken vigorously for one minute, and the layers were separated. The aqueous layer was further extracted with benzene (50ml.). The combined benzene extracts were added to 2,5-dimethylaniline (10.0g.) and the mixture boiled overnight in apparatus for continuously removing water from the reaction mixture (Dean and Stark apparatus). The solution was cooled and the benzene removed by evaporation under reduced pressure. The residual deep green liquid was added dropwise to diphenyl ether (200ml.) at 240°C. The mixture was heated at this temperature until no more ethanol was liberated (about 2 minutes) and the solution allowed to cool. It was diluted with petroleum ether (b.p. 40—60°C.; 1 l.) and the precipitated grey solid was filtered off, washed with petroleum ether (b.p. 40—60°C.) and recrystallised from cyclohexane (with carbon treatment) to give ethyl 5,8-dimethyl-4-hydroxyquinol-2-yl carboxylate, m.p. 108—109°C.

In a similar manner, using the appropriate starting materials, the following compounds were obtained:—



XIII

R	m.p. (°C.)	R	m.p. (°C.)
6-Br	254—255	6-$PhCH_2O$—	242—244
6,7-Me_2	233—235	5-Cl-8-Me—	137—139
8-n-BuO—	94—98	6-Cl-8-Me—	111—112
6-n-Bu	163—165	6,7-(i-PrO)$_2$	—
7,8-$(CH_2)_3$—	128—128.5	6-CH_3CO-3-Et	—

Example 12.

The method described in Example 11 was repeated, except that *m*-toluidine (90g.) was used as starting material in place of the 2,5-dimethylaniline. The crude product consisted of a mixture of two esters. This mixture (5g.) was separated chromatographically on a column of silica (1kg.; dimensions of column were 6 cm.× 100 cm.) eluted by chloroform containing a proportion of acetone increasing gradually from 5% to 20% v/v, to give ethyl 4-hydroxy-5-methylquinol-2-yl carboxylate, m.p. 192°C., and ethyl 4-hydroxy-7-methylquinol-2-yl carboxylate, m.p. 204°C.

Example 13.

Dimethyl acetylene dicarboxylate (6.2g.) was added dropwise to a stirred solution of *p*-benzylaniline (8.0g.) in methanol (40 ml.), the temperature being maintained below 30°C. When the addition was complete, the solution was refluxed for 2 hours. The solution was then cooled and the methanol evaporated off, leaving a green liquid. This was added to polyphosphoric acid (140g.), and the mixture was heated at 200°C. for 20 minutes. The solution was cooled, poured into a mixture of ice and water (1kg.), and the resulting white suspension was stirred for 10 minutes. It was then filtered, and the solid residue was washed with water and crystallised from 5% v/v aqueous dimethylformamide. There was thus obtained methyl 6-benzyl-4-hydroxyquinol-2-yl carboxylate, m.p. 195°C. (decomposition).

Example 14.

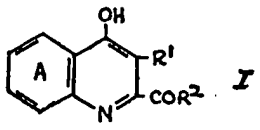
2,4-Dinitrophenetole (5.0g.) in ethanol (100ml.) was shaken with hydrogen in the presence of 5% w/w palladium on charcoal (0.5g.) at room temperature and atmospheric pressure until the amount of hydrogen absorbed corresponded to the reduction of one nitro group. The catalyst was filtered off and the filtrate evaporated. The residue was dissolved in methanol (50ml.), dimethyl acetylene dicarboxylate (7.3g.) was added, and the mixture was heated under reflux for two hours. The solvent was removed by distillation, the residue washed with ether, and filtered. The solid residue was crystallised from methanol to give *N*-[1,2-bis(methoxycarbonyl)vinyl]-2-ethoxy-5-nitroaniline, m.p. 158—160°C.

This compound was cyclised by heating in diphenyl ether by the method of Example 11 to give methyl 8-ethoxy-4-hydroxy-5-nitroquinol-2-yl carboxylate, m.p. 226—227°C. (crystallised from dioxan).

Example 15.

A solution of the nitro ester described in Example 14 (0.6g.) in dimethylformamide (25 ml.) was shaken with hydrogen in the presence of 5% w/w palladium on charcoal (0.1g.) for 15 minutes. The hydrogen uptake was 150 ml. (theory 140 ml.). The catalyst was filtered off and the filtrate poured into water (100 ml.). The mixture was filtered and the residue crystallised from methanol to give methyl 5-amino-8-ethoxy-4-hydroxyquinol-2-yl carboxylate, m.p. 164—165°C.

It is to be understood that in this specification no claim is made to the following known compounds or non-toxic pharmaceutically-acceptable salts thereof, to pharmaceutical compositions comprising one of the said known compounds or salts thereof, or to chemical processes for making any of the said known compounds or salts thereof: —



I

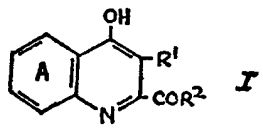
R^1	R^2	A
H	OEt	6,7-$(MeO)_2$
Me	OEt	H
H	OH	6,7-$(MeO)_2$
Me	OEt	6-MeO
Me	OH	6-MeO
Me	OEt	6,8-Me_2
Me	OEt	6,7-$(MeO)_2$
Me	OEt	6-Cl
H	OEt	H
Me	OEt	5,6-Cl_2

It is also to be understood that in this specification no claim is made to the following known compounds or non-toxic pharmaceutically-acceptable salts thereof, or to processes for the manufacture thereof: — 4-hydroxyquinol-2-yl carboxylic acid and its methyl ester, 4-hydroxy-8-methylquinol-2-yl carboxylic acid, 4-hydroxy-6-methylquinol-2-yl carboxylic acid and its ethyl ester, methyl 4-hydroxy-6,8-dimethylquinol-2-yl carboxylate, 4-hydroxy-7-methoxyquinol-2-yl carboxylic acid, 4-hydroxy-6-methoxyquinol-2-yl carboxylic acid and its ethyl ester, 4-hydroxy-8-methoxyquinol-2-yl carboxylic acid and its methyl and ethyl esters, 4-hydroxy-5,6-dimethoxyquinol-2-yl carboxylic acid and its ethyl ester, 4-hydroxy-5,8-dimethoxyquinol-2-yl carboxylic acid and its ethyl ester, methyl 4-hydroxy-6,7-dimethoxyquinol-2-yl carboxylate, ethyl 4-hydroxy-7,8-dimethoxyquinol-2-yl carboxylate, 6-bromo-4-hydroxyquinol-2-yl carboxylic acid, 7-bromo-4-hydroxyquinol-2-yl carboxylic acid and its ethyl ester, 8-bromo-4-hydroxyquinol-2-yl carboxylic acid, 5-chloro-4-hydroxyquinol-2-yl carboxylic acid, and its methyl and ethyl esters, 6-chloro-4-hydroxyquinol-2-yl carboxylic acid and its methyl ester, 7-chloro-4-hydroxyquinol-2-yl carboxylic acid and its methyl and ethyl esters, methyl 8-chloro-4-hydroxyquinol-2-yl carboxylate, 4-hydroxy-7-iodoquinol-2-yl carboxylic acid and its ethyl ester, methyl and ethyl 6-fluoro-4-hydroxyquinol-2-yl carboxylate, 5,7-dibromo-4-hydroxyquinol-2-yl carboxylic acid and its ethyl ester, 5,6-dichloro-4-hydroxyquinol-2-yl carboxylic acid and its ethyl ester, 5,7-dichloro-4-hydroxyquinol-2-yl carboxylic acid and its methyl and ethyl esters, 5,8-dichloro-4-hydroxyquinol-2-yl carboxylic acid and its ethyl ester, 6,7-dichloro-4-hydroxyquinol-2-yl carboxylic acid and its ethyl ester, 6,8-dichloro-4-hydroxyquinol-2-yl carboxylic acid and its ethyl ester, 4-hydroxy-3-methylquinol-2-yl carboxylic acid, 1-hydroxybenzo(f)quinol-3-yl carboxylic acid and its ethyl ester, 1-hydroxy-7-methoxybenzo(f)quinol-3-yl carboxylic acid and its ethyl ester, 1-hy-

droxy-10-methoxybenzo(f)quinol-3-yl carboxylic acid and its ethyl esters, ethyl 1-hydroxy-8-methoxybenzo(f)quinol-3-yl carboxylate, 4-hydroxybenzo(h)quinol-2-yl carboxylic acid and its ethyl ester, 4-hydroxy-6-methoxybenzo(h)quinol-2-yl carboxylic acid and its ethyl ester, 7,8,9,10-tetrahydro-4-hydroxy-6-methoxybenzo(h)quinol-2-yl carboxylic acid and its ethyl ester, 4-hydroxy-7-methoxy-8-nitroquinol-2-yl carboxylic acid, 5-amino-4-hydroxyquinol-2-yl carboxylic acid, 6-amino-4-hydroxyquinol-2-yl carboxylic acid, 7-chloro-4-hydroxy-6-methoxyquinol-2-yl carboxylic acid and its methyl and ethyl esters, methyl 8-acetyl-4-hydroxyquinol-2-yl carboxylate, 6-acetyl-4-hydroxyquinol-2-yl carboxylic acid and its ethyl ester, methyl 6-chloro-4-hydroxy-8-nitroquinol-2-yl carboxylate, 4-hydroxy-6-methoxy-8-nitroquinol-2-yl carboxylic acid and its methyl ester, methyl 4-hydroxy-6-methyl-8-nitroquinol-2-yl carboxylate, methyl and ethyl 4-hydroxy-6-nitroquinol-2-yl carboxylate, methyl 4-hydroxy-7-nitroquinol-2-yl carboxylate, 4-hydroxy-8-nitroquinol-2-yl carboxylic acid and its methyl ester, 6-benzyl-4-hydroxyquinol-2-yl carboxylic acid and its ethyl ester, 7-chloro-4-hydroxy-8-methylquinol-2-yl carboxylic acid and its ethyl ester, 5-bromo-4-hydroxy-6-methoxyquinol-2-yl carboxylic acid and its ethyl ester, 7-bromo-4-hydroxy-6-methoxyquinol-2-yl carboxylic acid and its ethyl ester, 4-hydroxy-5-iodo-8-methoxyquinol-2-yl carboxylic acid, methyl 4-hydroxy-6-methoxy-7-trifluoromethylquinol-2-yl carboxylate, methyl 8-chloro-4-hydroxy-5-trifluoromethylquinol-2-yl carboxylate, methyl 5-chloro-4-hydroxy-6-methoxyquinol-2-yl carboxylate, methyl 7-fluoro-4-hydroxy-6-methoxyquinol-2-yl carboxylate, 4-hydroxy-3,5-dimethylquinol-2-yl carboxylic acid and its ethyl ester, 4-hydroxy-3,6-dimethylquinol-2-yl carboxylic acid and its ethyl ester, 4-hydroxy-3,7-dimethylquinol-2-yl carboxylic acid and its ethyl ester, 4-hydroxy-3,8-dimethylquinol-2-yl carboxylic acid and its ethyl ester, 4-hydroxy-3,5,6-trimethylquinol-2-yl carboxylic acid and its ethyl ester, 4-hydroxy-3,6,7-trimethylquinol-2-yl carboxylic acid, 6-ethoxy-4-hydroxy-3-methylquinol-2-yl carboxylic acid and its ethyl ester, 8-ethoxy-4-hydroxy-3-methylquinol-2-yl carboxylic acid and its ethyl ester, 7-ethoxy-4-hydroxy-3-methylquinol-2-yl carboxylic acid and its ethyl ester, 4-hydroxy-7-methoxy-3-methylquinol-2-yl carboxylic acid and its ethyl ester, 4-hydroxy-8-methoxy-3-methylquinol-2-yl carboxylic acid and its ethyl ester, ethyl 4-hydroxy-6,8-dimethoxy-3-methylquinol-2-yl carboxylate, 5-bromo-4-hydroxy-3-methylquinol-2-yl carboxylic acid and its ethyl ester, 5-chloro-4-hydroxy-3-methylquinol-2-yl carboxylic acid and its ethyl ester, 7-bromo-4-hydroxy-3-methylquinol-2-yl carboxylic acid and its ethyl ester, 7-chloro-4-hydroxy-3-methylquinol-2-yl carboxylic acid and its ethyl ester, 6-chloro-4-hydroxy-3-methylquinol-2-yl carboxylic acid, 6-bromo-4-hydroxy-3-methylquinol-2-yl carboxylic acid and its ethyl ester, 8-chloro-4-hydroxy-3-methylquinol-2-yl carboxylic acid and its ethyl ester, 8-bromo-4-hydroxy-3-methylquinol-2-yl carboxylic acid and its ethyl ester, ethyl 4-hydroxy-5-iodo-3-methylquinol-2-yl carboxylate, 4-hydroxy-6-iodo-3-methylquinol-2-yl carboxylic acid and its ethyl ester, 4-hydroxy-7-iodo-3-methylquinol-2-yl carboxylic acid and its ethyl ester, 4-hydroxy-8-iodo-3-methylquinol-2-yl carboxylic acid and its ethyl ester, 5-fluoro-4-hydroxy-3-methylquinol-2-yl carboxylic acid and its ethyl ester, 6-fluoro-4-hydroxy-3-methylquinol-2-yl carboxylic acid and its ethyl ester, 7-fluoro-4-hydroxy-3-methylquinol-2-yl carboxylic acid and its ethyl ester, 8-fluoro-4-hydroxy-3-methylquinol-2-yl carboxylic acid and its ethyl ester, 8-chloro-4-hydroxy-3,5-dimethylquinol-2-yl carboxylic acid and its ethyl ester, 4-hydroxy-3-methyl-5-trifluoromethylquinol-2-yl carboxylic acid and its ethyl ester, 4-hydroxy-3-methyl-7-trifluoromethylquinol-2-yl carboxylic acid and its ethyl ester, ethyl 4-hydroxy-3-methyl-5-nitroquinol-2-yl carboxylate, 4-hydroxy-3-methyl-6-nitroquinol-2-yl carboxylic acid and its ethyl ester, and ethyl 4-hydroxy-3-methyl-7-nitroquinol-2-yl carboxylate.

Subject to the foregoing disclaimers, WHAT WE CLAIM IS:—

1. A pharmaceutical composition comprising a compound of the formula:—

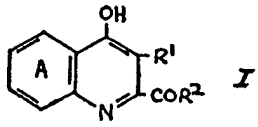


I

wherein R^1 stands for hydrogen, a methyl or ethyl radical, or a halogen atom, R^2 stands for a hydroxy or C_{1-6} alkoxy radical, and the benzene ring A optionally bears not more than two substituents selected from C_{1-5} alkyl, C_{1-5} alkoxy, benzyl, phenyl,

benzyloxy, acetyl, halogen, trifluoromethyl, nitro and amino radicals, or wherein the said benzene ring A is optionally fused with an unsubstituted benzene ring ,a methoxy-substituted-benzene ring or a tetramethylene radical, or a non-toxic pharmaceutically-acceptable salt thereof, and an inert non-toxic pharmaceutically-acceptable diluent or carrier.

2. A pharmaceutical composition comprising a compound of the formula:—



I

wherein R^1 stands for hydrogen, a methyl or ethyl radical, or a halogen atom, R^2 stands for a hydroxy or C_{1-6} alkoxy radical, and the benzene ring A optionally bears a substituent selected from C_{1-5} alkyl, C_{1-5} alkoxy, benzyl, phenyl, benzyloxy, acetyl, halogen, trifluoromethyl, nitro and amino radicals, or wherein the said benzene ring A is optionally fused with an unsubstituted benzene ring or a methoxy-substituted-benzene ring, or a non-toxic pharmaceutically-acceptable salt thereof, and an inert non-toxic pharmaceutically-acceptable diluent or carrier.

3. A composition as claimed in claim 1 wherein R^1 stands for hydrogen, a methyl or ethyl radical, or a fluorine, chlorine, bromine or iodine atom, R^2 stands for a hydroxy, methoxy or ethoxy radical, and the benzene ring A optionally bears one or two substituents selected from methyl, ethyl, propyl, butyl, methoxy, ethoxy, propoxy, butoxy, benzyl, phenyl, benzyloxy, acetyl, fluorine, chlorine, bromine, iodine, trifluoromethyl, nitro and amino radicals, or it is optionally fused with an unsubstituted benzene ring, a methoxy substituted-benzene ring or a tetramethylene radical.

4. A composition as claimed in any of claims 1 to 3 wherein the said compound of formula I is present as a non-toxic pharmaceutically-acceptable acid-addition salt or as a salt in which the cationic moiety is non-toxic and pharmaceutically-acceptable.

5. A composition as claimed in claim 4 in which the salt is an ammonium, alkali metal, alkaline earth metal, or aluminium salt, or a salt with piperidine, triethanolamine or ethylenediamine.

6. A composition as claimed in claim 2 in which the active ingredient is 4-hydroxy-7,8-dimethylquinol-2-yl carboxylic acid or 4-hydroxy-7-methylquinol-2-yl carboxylic acid.

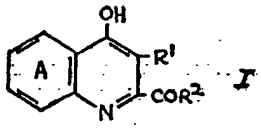
7. A composition as claimed in claim 1 in which the active ingredient is 4-hydroxy-8-nitroquinol-2-yl carboxylic acid or 1-hydroxybenzo(f)quinol-3-yl carboxylic acid.

8. A composition as claimed in any one of claims 1 to 7 which is in a form suitable for administration by inhalation.

9. A composition as claimed in any one of claims 1 to 8 which contains, in addition to a compound of formula I, one or more other active ingredients selected from β-adrenergic stimulants, known prostaglandins having bronchodilatory activity, and/or a phosphodiesterase inhibitor selected from the following compounds:—
(a) 3-acetamido-6-methyl-8-n-propyl-2-triazolo[4,3-a]pyrazine,
(b) 2-amino-4,6-di-C_{1-4}-alkyl-5-oxo-4,5 - dihydro-s-triazolo[1,5-a]pyrimidine derivatives, (c) theophylline and related 3,5-di-C_{1-4}-alkylxanthine derivatives, and (d) 6,8-di-C_{1-4}-alkyl-5,6-dihydro-5-oxo-s-triazolo[4,3-c]pyrimidine derivatives.

10. A composition as claimed in any of claims 1 to 9 which contains 1% to 50% by weight of a compound of formula I wherein A, R^1 and R^2 have the meanings stated in claim 1, or a non-toxic pharmaceutically-acceptable salt thereof.

11. A compound of the formula:—



I

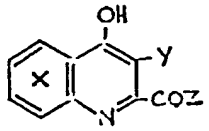
wherein R^1 stands for hydrogen or a methyl or ethyl radical, R^2 stands for a hydroxy or C_{1-6} alkoxy radical, and the benzene ring A is optionally substituted with not more than two substituents selected from C_{1-5} alkyl, C_{1-5} alkoxy, benzyl, benzyloxy, acetyl, halogen, trifluoromethyl, nitro or amino radicals, or wherein the benzene ring A is optionally fused in the 5,6- or 7,8-position with an unsubstituted benzene ring, a

methoxy-substituted benzene ring or a tetramethylene radical, or a non-toxic pharmaceutically-acceptable salt thereof.

12. 4-Hydroxy-7,8-dimethylquinol-2-yl carboxylic acid or a non-toxic pharmaceutically-acceptable salt thereof.

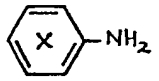
13. 4-Hydroxy-7-methylquinol-2-yl carboxylic acid or a non-toxic pharmaceutically-acceptable salt thereof.

14. A process for the manufacture of those of the new compounds claimed in claim 11 wherein R^2 stands for a C_{1-6} alkoxy radical, which compounds have the formula:—



VII

wherein X and Y correspond to A and R^1 respectively as defined in claim 11, and Z stands for a C_{1-6} alkoxy radical, which comprises carrying out the Conrad-Limpach reaction on an arylamine of the formula:—



VIII

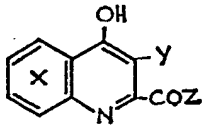
and a compound of the formula:—

Z.CO.CHY.CO.COZ IX

wherein X, Y and Z have the meanings stated immediately above.

15. A process as claimed in claim 14 in which the first stage of the Conrad-Limpach reaction is carried out at 80—100°C. in an aromatic hydrocarbon solvent under reaction conditions which facilitate the removal of water from the reaction mixture, and in which the second stage of the reaction is carried out by heating the intermediate compound at 230—250°C., or by heating it with polyphosphoric acid at 130—180°C.

16. A process for the manufacture of compounds of the formula:—



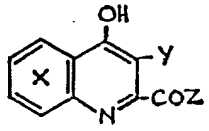
VII

wherein X has the meaning stated in claim 14, Y stands for hydrogen, and Z stands for a C_{1-6} alkoxy radical, which comprises reacting an arylamine of the formula VIII with an acetylene derivative of the formula:—

ZOC.C≡C.COZ XI

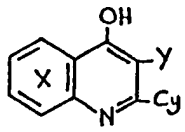
in the presence of an alkanol of the formula ZOH, and, following an optional initial stage during which the temperature of the reaction mixture is not allowed to exceed 30°C., under the influence of heat, so as to give a compound which in one of its tautomeric forms has the formula X, and then heating this compound at 230—250°C., or heating it with polyphosphoric acid at 130—180°C., and wherein X, Y and Z have the meanings stated immediately above.

17. A process for the manufacture of those of the new compounds claimed in claim 11 wherein R^2 stands for a hydroxy radical, which compounds have the formula:—



VII

wherein X and Y correspond to A and R^1 respectively as defined in claim 11, and Z stands for a hydroxy radical, which comprises hydrolysing a compound of the formula:—



XII

wherein X and Y have the meanings stated immediately above, and Cy stands for a C_{2-7} alkoxycarbonyl, C_{8-11} phenylalkoxycarbonyl, phenoxycarbonyl, cyano, carbamoyl or thiocarbamoyl radical.

18. A process as claimed in claim 17 in which the hydrolytic agent is an alkali metal hydroxide or an inorganic acid.

19. A process for the manufacture of those of the new compounds claimed in claim 11 wherein the benzene ring A bears one or two amino radicals and R^2 stands for a C_{1-6} alkoxy radical, which comprises catalytically reducing the nitro group or groups in the corresponding nitro derivative.

20. A pharmaceutical composition, claimed in claim 1, substantially as described hereinbefore in any of Examples 1 to 3.

21. A compound, claimed in claim 11, substantially as described hereinbefore in any of Examples 4 to 15.

22. A process, claimed in claim 14, 16, 17 or 19, substantially as described hereinbefore in any of Examples 4 to 15.

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